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Cortical Thickness in Individuals at High Familial Risk of Mood Disorders as They Develop Major Depressive Disorder

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Cortical Thickness in Individuals at High Familial Risk of Mood Disorders as They Develop Major Depressive Disorder

Martina Papmeyer, Stephen Giles, Jessica E. Sussmann, Shauna Kielty, Tiffany Stewart,
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ABSTRACT

BACKGROUND: Frontal and temporal cortical thickness abnormalities have been observed in mood disorders. However, it is unknown whether cortical thickness abnormalities reflect early adverse effects of genetic and environmental risk factors predisposing to mood disorders or emerge at illness onset.

METHODS: Magnetic resonance imaging was conducted at baseline and after a 2-year follow-up interval in 111 initially unaffected young adults at high familial risk of mood disorders and 93 healthy control subjects (HC). During the follow-up period, 20 high-risk subjects developed major depressive disorder (HR-MDD), with the remainder remaining well (HR-well). Cortical surface reconstruction was applied to measure cortical thickness of frontal and temporal regions of interest. Mixed-effects models were used to investigate differences and longitudinal changes in cortical thickness.

RESULTS: Reduced cortical thickness in the right parahippocampal and fusiform gyrus across both time points was found in both high-risk groups. HR-MDD also had thinner parahippocampi than HR-well individuals. Over time, HR-well and HC individuals had progressive thickness reductions in the left inferior frontal and precentral gyrus, which were greater in HR-well subjects. HR-MDD showed left inferior frontal gyrus thickening relative to HR-well subjects and left precentral gyrus thickening relative to HR-well and HC individuals.

CONCLUSIONS: Reduced right parahippocampal and fusiform gyrus thickness are familial trait markers for vulnerability to mood disorders. Increased risk for mood disorders is associated with progressive cortical thinning in the left inferior frontal and precentral gyri in subjects who remain well. In contrast, onset of depression is associated with increasing left inferior frontal and precentral thickness.

Keywords: Bipolar disorder, Cortical thickness, High risk, Longitudinal, Magnetic resonance imaging, Major depressive disorder

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Mood disorders including bipolar disorder (BD) and major depressive disorder (MDD) are among the most common mental disorders and a leading cause of disability worldwide (1). First-degree relatives of BD patients have a tenfold excess risk of BD compared with the general population and a threefold increased risk of MDD (2). The aggregation of mood disorders within families together with moderate to high heritability estimates and evidence of a shared genetic architecture provide strong support for overlapping causal pathways in BD and MDD (3–6).

Accumulating evidence from structural magnetic resonance imaging (MRI) studies indicates that neuroanatomical changes in frontal and temporal lobes are associated with mood disorders (7–10). Volumetric gray matter reductions of the prefrontal lobe have been consistently found in MDD and BD, predominantly in the orbitofrontal gyrus (8,11) and anterior cingulate cortex (10,12) but also in the inferior (10,12), middle (10,13), and superior frontal gyrus (10,14). Furthermore, gray

matter decreases have been observed in the precentral gyrus (10,13), superior temporal gyrus (15,16), and medial temporal lobe, particularly in the parahippocampal gyrus (10,17).

Gray matter volume is a composite of cortical thickness and surface area, and research suggests that gray matter volume is more closely linked to surface area than to thickness (18). Cortical surface area and thickness are also genetically and phenotypically independent (18), but the contribution of cortical thickness toward structural brain abnormalities in mood disorders remains largely unknown. A small number of studies have, however, reported cortical thickness abnormalities in MDD and BD patients in the frontal lobe (19–31) and superior temporal gyrus (22,23,29,31). Moreover, thickness reductions in the inferior and middle temporal (31), parahippocampal (22), and fusiform gyrus (21,23) have been found in BD.

Prefrontal brain regions are closely involved in emotion processing and affect regulation—functions clearly disturbed in mood disorders (32,33). Distinct frontal lobe structures

maintain reciprocal connections to temporal brain areas and are intensively interconnected with limbic regions. Accordingly, it has been postulated that a medial prefrontal network, highly connected to superior and medial temporal lobe, is centrally involved in mood disorders (34,35).

Most imaging studies of mood disorders have assessed brain structure in affected individuals. These studies cannot discern whether structural brain abnormalities reflect early neurodevelopmental disruptions predisposing to illness, events linked to illness onset, or whether they are adaptive or secondary to the effects of chronic illness or its treatment. Neuroimaging studies of individuals at high risk of mood disorders because of a close family history of BD hold the potential to identify structural brain abnormalities related to enhanced familial vulnerability, unconfounded by the presence of illness and medication. However, to the best of our knowledge, no study has yet examined the effects of familial risk on cortical thickness in a prospective longitudinal study.

The Bipolar Family Study is designed to examine the timing of structural brain abnormalities in mood disorders and their relationship to familial risk and onset of illness. Based on the above literature, we compared cortical thickness of frontal and temporal regions of interest (ROI) over a 2-year time interval between three groups: high-risk of mood disorders individuals who were well at baseline but developed MDD during the follow-up period (HR-MDD), high-risk individuals who remained well over the same time period (HR-well), and unaffected healthy control subjects (HC). We hypothesized that frontotemporal cortical thickness reductions related to familial risk of mood disorders are present before the onset of illness. Furthermore, we hypothesized that these regions reduce in thickness progressively in the 2-year period before illness and that an onset of MDD is associated with more pronounced thickness reductions as compared with individuals who remain well.

METHODS AND MATERIALS

Participants

Participants were recruited as part of the Bipolar Family Study (36). High-risk of mood disorder individuals because of a close family history of BD were identified via affected relatives (Supplement 1). Unaffected, unrelated control subjects with no personal or family history of BD were identified from the social contacts of the high-risk subjects and group-matched for age, sex, and premorbid intelligence estimated with the National Adult Reading Test (37). Comparison subjects were screened for Axis I disorders using the Structured Clinical Interview for DSM-IV Axis I Disorders.

At baseline, exclusion criteria for all study groups included a personal history of MDD, mania or hypomania, psychosis, or any major neurological or psychiatric disorder; substance dependence; learning disability; head injury that included loss of consciousness; and any contraindications to MRI.

Approximately 2 years after the initial baseline examination, all participants were invited for a follow-up assessment. Written informed consent was acquired from all subjects and the study was approved by the Research Ethics Committee for Scotland.

Clinical Assessment

Clinical assessments were conducted at the time of the first and second MRI scans. The mean interval in years between assessments was 2.13 (SD .22), 2.15 (SD .22), and 2.10 (SD .13) for the HC, HR-well, and HR-MDD groups, respectively. The diagnostic status of consenting subjects not returning for a second assessment was determined through written contact with the National Health Service. Clinical interviews were conducted by experienced psychiatrists (A.M.M., J.E.S.). Based on the follow-up clinical examination or information from case notes, high-risk subjects were grouped into those who remained well (HR-well) and those who subsequently developed MDD (HR-MDD). At both assessments, current manic and depressive symptoms were rated using the Young Mania Rating Scale (38) and Hamilton Depression Rating Scale (HAM-D) (39).

Statistical analyses of demographic and clinical data were conducted using one-way analyses of variance (ANOVAs), chi-squares tests, or Kruskal-Wallis tests where appropriate in SPSS version 19 (<http://www.spss.com>).

Magnetic Resonance Imaging Acquisition

Imaging at baseline and follow-up assessment were carried out at the Brain Imaging Research Centre for Scotland on a GE 1.5 T Signa scanner (GE Medical, Milwaukee, Wisconsin). The T1 sequence was a coronal gradient echo sequence with magnetization preparation (magnetization prepared rapid acquisition gradient-echo) and yielded 180 contiguous 1.2 mm coronal slices (inversion time = 500 msec; echo time = 4 msec; matrix = 192 × 192; flip angle = 8°).

Cortical Thickness Measurement

The acquired T1 images were processed using the surface-based stream in FreeSurfer version 5.1.0 (<http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all/>) (40,41), fully described in Supplement 1.

The following ROIs were selected for each hemisphere (Figure 1): anterior cingulate cortex (rostral and caudal anterior cingulate cortex), frontal pole, inferior frontal gyrus (pars opercularis, triangularis, and orbitalis), middle frontal gyrus (rostral and caudal middle frontal gyrus), superior frontal gyrus, orbitofrontal gyrus (lateral and medial orbitofrontal gyrus), precentral gyrus, superior temporal gyrus, parahippocampal gyrus, and fusiform gyrus.

Statistical Analyses

All statistical analyses were computed in SPSS version 19, except for the false discovery rate (FDR) corrections (42), which were conducted in R version 2.13.0 (<http://www.r-project.org>), using the p.adjust(BH) function of the stats package.

Given the longitudinal study design and the fact that the data consist of nonuniform numbers of repeated measurements, we performed linear mixed-effects models to investigate structural brain differences for each ROI over time. Linear mixed-effects modeling has several advantages over the commonly applied repeated-measures ANOVA, as case-wise deletion of missing data is not necessary, which allows the analysis of all available data. Moreover, it handles the

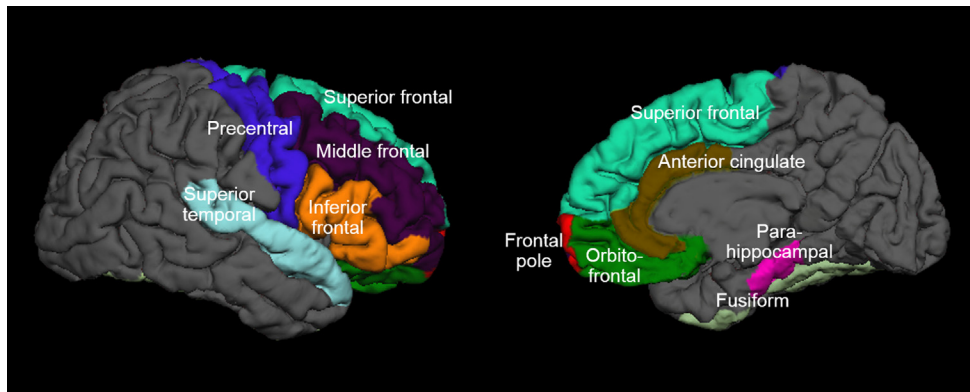


Figure 1. Cortical regions of interest.

correlation structures of repeated measurements nested within participants. In the linear mixed-effects model used, the intercept term is treated as a random effect that varies by individual so that intraindividual correlation among the structural brain measures of a particular individual is taken into account. The following independent variables were used as predictors of cortical thickness for the different ROIs: group, time (baseline versus follow-up assessment), and group-by-time interaction. Age and sex served as covariates. Accordingly, significant group effects represent differences in cortical thickness between the groups across both time points. Time effects represent differences in cortical thickness between baseline and follow-up examination. Group-by-time interactions represent differences in cortical thickness development over time between groups.

A statistical significance level of $p_{FDR} \leq .05$ was chosen, fully corrected for multiple comparisons using the Benjamini and Hochberg FDR procedure (42). Wherever significant between-group differences were found, pairwise comparisons were performed between the three groups for which p values were corrected according to Tukey's honest significance difference (HSD) method ($p_{HSD} \leq .05$). For significant interaction effects, subsequent pairwise comparisons were performed with p values being adjusted according to Bonferroni procedure ($p_{Bonf} \leq .05$).

Wherever significant between-group differences were found in the longitudinal analysis, an additional analysis of covariance was conducted between the groups for cortical thickness of the ROI at baseline, adjusted for age and sex. This analysis was intended to assess whether the observed longitudinal ROI abnormalities were also predictive at baseline for an onset of MDD.

To assess the relationship between severity of depressive symptoms and cortical thickness, we calculated the Spearman correlation coefficient between the HAM-D total score and the ROIs for each group. In each case, p values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

To examine potentially confounding effects of exposure to medication and relatedness of subjects on cortical thickness, we performed the following additional analyses for significant findings: we first repeated our analyses excluding medicated HR-MDD subjects ($n = 4$), followed by randomly excluding related subjects ($n = 2$ HC; $n = 17$ HR-well; $n = 2$ HR-MDD).

RESULTS

Demographic and Clinical Measures

In total, 114 high-risk individuals provided suitable FreeSurfer processed MRI data along with clinical information at baseline. Of these, two individuals developed BD during the 2-year follow-up period and were excluded from all analyses due to the small sample size. Overall, 20 high-risk participants received a diagnosis of MDD within the 2-year period, but one individual had to be excluded from baseline analysis due to unsatisfactory cortical parcellation of the MRI scan. Accordingly, our analyses included 92 HR-well and 19 HR-MDD subjects at baseline. Of the HC individuals, 96 provided suitable MRI data along with clinical information at baseline. Three developed MDD in the follow-up period and were therefore excluded from all analyses, leading to a sample size of 93 HC subjects. At follow-up, 63 HR-well, 20 HR-MDD, and 62 HC subjects provided suitable data. Four HR-MDD participants were prescribed antidepressant medication at follow-up. Three subjects were taking selective serotonin reuptake inhibitors (1 fluoxetine, 1 citalopram, 1 sertraline) and one participant was on a tricyclic antidepressant (lofepramine). The remaining 16 HR-MDD subjects were unmedicated.

There were no significant differences between the groups in terms of age, gender, handedness, verbal intelligence, and Young Mania Rating Scale sum score at any assessment point (Table 1). There were, however, significant group differences at baseline ($p \leq .007$) and follow-up ($p \leq .023$) for clinical measures of depression from the HAM-D. At baseline, HR-well and HR-MDD subjects had significantly higher depression scores ($p \leq .047$ and $p \leq .003$, respectively) than HC individuals, with no significant differences between the high-risk groups. At follow-up, HR-MDD subjects had higher depression scores than HC and HR-well individuals ($p \leq .013$ and $p \leq .010$, respectively), as expected, with no significant differences between HC and HR-well individuals.

Cortical Thickness

Table 2 and Figure 2 depict the results of our linear mixed-effects model analyses. A significant group effect ($p_{FDR} \leq .05$) was found for the right parahippocampal gyrus ($p \leq .002$) and right fusiform gyrus ($p \leq .005$). Post hoc analyses revealed that HR-well ($p_{HSD} \leq .049$) and HR-MDD ($p_{HSD} \leq .011$)

Table 1. Demographic and Clinical Characteristics

	Baseline					Follow-up				
	HC (n = 93)	HR-well (n = 92)	HR-MDD (n = 19)	Statistics		HC (n = 62)	HR-well (n = 63)	HR-MDD (n = 20)	Statistics	
	Mean (SD)	Mean (SD)	Mean (SD)	F/χ^2	p	Mean (SD)	Mean (SD)	Mean (SD)	F/χ^2	p
Age (Years)	21.01 (2.45)	21.20 (2.88)	21.10 (2.82)	.13	.88	22.82 (2.73)	23.71 (2.84)	23.33 (2.98)	1.77	.17
Gender (M:F)	40:53	44:48	9:10	.46	.80	21:41	29:34	7:13	2.12	.35
Handedness (Right:Other)	88:5	81:11	19:0	5.54	.24	61:1	57:6	20:0	5.43	.07
NART IQ	110.31 (8.00)	108.39 (9.37)	107.26 (6.80)	1.64	.20	–	–	–	–	–
ISI (Months)	2.13 (.22)	2.15 (.22)	2.10 (0.13)	.20	.82	–	–	–	–	–
HAM-D ^a	0 (1)	0 (2)	1 (5)	9.79	.01	1 (3)	1 (2)	5 (12)	7.59	.02
YMRS ^a	0 (0)	0 (0)	0 (0)	3.48	.18	0 (0)	0 (1)	0 (0)	.79	.68

Bold indicates significant effect.

F, female; HAM-D, Hamilton Depression Rating Scale; HC, unaffected healthy control subjects; HR, high risk; HR-MDD, individuals at high risk for mood disorders who were well at baseline but developed major depressive disorder during the follow-up period; HR-well, individuals at high risk for mood disorders who were well at baseline and remained well during the follow-up period; ISI, interscan interval; M, male; MDD, major depressive disorder; NART, National Adult Reading Test; YMRS, Young Mania Rating Scale.

^aKruskal-Wallis test, median and interquartile presented for skewed variables.

individuals have reduced parahippocampal thickness across time as compared with HC subjects. This brain region was, on average, 4.00% thinner in the HR-well and 10.89% thinner in the HR-MDD group relative to control subjects across both time points. Moreover, HR-MDD subjects displayed more pronounced thickness reductions in this region as compared

with the HR-well ($p_{\text{HSD}} \leq .041$) group. For the right fusiform gyrus, HR-well ($p_{\text{HSD}} \leq .028$) and HR-MDD ($p_{\text{HSD}} \leq .014$) subjects have reduced cortical thickness as compared with HC individuals, with no significant difference between the high-risk groups. The fusiform gyrus was, on average, 2.11% thinner in the HR-well and 4.22% thinner in the HR-MDD

Table 2. Longitudinal Analysis of Cortical Thickness

Region (Gyrus)	HC		HR-well		HR-MDD		Statistics					
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Group Effect		Time Effect		Group \times Time	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	F	p	F	p
L Inf Frontal G	2.47 (.22)	2.44 (.17)	2.49 (.15)	2.40 (.17)	2.52 (.20)	2.55 (.22)	3.14	.05	3.22	.08	5.35	<.01
R Inf Frontal G	2.46 (.17)	2.44 (.19)	2.42 (.15)	2.42 (.17)	2.50 (.21)	2.45 (.18)	1.69	.19	3.51	.06	1.30	.28
L Mid Frontal G	2.38 (.18)	2.39 (.16)	2.42 (.16)	2.39 (.17)	2.43 (.19)	2.51 (.16)	3.41	.04	.93	.34	1.80	.15
R Mid Frontal G	2.35 (.16)	2.33 (.17)	2.34 (.14)	2.34 (.16)	2.39 (.20)	2.39 (.16)	1.54	.22	.57	.45	.47	.71
L Sup Frontal G	2.70 (.18)	2.69 (.19)	2.70 (.18)	2.68 (.18)	2.72 (.18)	2.81 (.20)	2.40	.10	.10	.76	1.04	.38
R Sup Frontal G	2.65 (.19)	2.61 (.17)	2.64 (.19)	2.61 (.18)	2.70 (.19)	2.74 (.17)	3.11	.05	.34	.56	1.65	.18
L Orbitofrontal G	2.44 (.23)	2.39 (.20)	2.45 (.20)	2.41 (.17)	2.42 (.28)	2.48 (.20)	.73	.48	.39	.54	2.66	.05
R Orbitofrontal G	2.41 (.23)	2.39 (.20)	2.38 (.19)	2.38 (.19)	2.40 (.21)	2.42 (.19)	.24	.79	.04	.85	.79	.50
L Frontal Pole	2.95 (.40)	2.95 (.41)	3.03 (.43)	3.03 (.38)	3.06 (.38)	3.20 (.43)	3.00	.05	.73	.40	.44	.73
R Frontal Pole	2.90 (.41)	2.87 (.40)	2.84 (.36)	2.85 (.31)	3.08 (.34)	3.06 (.44)	2.94	.02	.20	.66	.22	.88
L Ant Cingulate	2.48 (.33)	2.46 (.29)	2.47 (.32)	2.44 (.28)	2.48 (.33)	2.54 (.29)	.22	.80	.00	1.00	1.57	.20
R Ant Cingulate	2.39 (.31)	2.37 (.26)	2.43 (.32)	2.35 (.29)	2.43 (.36)	2.42 (.23)	.25	.78	1.88	.17	1.90	.13
L Precentral G	2.49 (.14)	2.45 (.13)	2.49 (.13)	2.43 (.15)	2.48 (.18)	2.53 (.12)	2.10	.34	2.83	.10	8.67	<.01
R Precentral G	2.45 (.12)	2.43 (.14)	2.44 (.13)	2.42 (.15)	2.44 (.14)	2.46 (.16)	.51	.60	2.02	.16	2.19	.09
L Fusiform G	2.33 (.21)	2.29 (.18)	2.32 (.18)	2.27 (.18)	2.29 (.21)	2.24 (.30)	1.04	.35	3.35	.07	1.72	.17
R Fusiform G	2.37 (.18)	2.38 (.17)	2.31 (.22)	2.33 (.19)	2.25 (.19)	2.29 (.23)	5.20	<.01	.66	.42	.23	.88
L Sup Temporal G	2.42 (.22)	2.43 (.21)	2.45 (.19)	2.41 (.20)	2.45 (.18)	2.41 (.25)	.04	.96	.98	.32	1.03	.38
R Sup Temporal G	2.44 (.19)	2.50 (.18)	2.42 (.21)	2.43 (.21)	2.40 (.18)	2.40 (.18)	3.60	.03	.50	.48	1.55	.21
L Parahippoc G	2.24 (.34)	2.25 (.32)	2.19 (.34)	2.12 (.37)	2.14 (.37)	2.13 (.45)	1.76	.17	1.73	.19	1.43	.24
R Parahippoc G	2.23 (.34)	2.27 (.29)	2.15 (.35)	2.17 (.31)	1.98 (.32)	2.03 (.37)	6.27	<.01	.44	.51	.20	.90

Bold indicates significant effect after false discovery rate correction.

G, gyrus; HC, unaffected healthy control subjects; HR, high risk; HR-MDD, individuals at high risk for mood disorders who were well at baseline but developed major depressive disorder during the follow-up period; HR-well, individuals at high risk for mood disorders who were well at baseline and remained well during the follow-up period; inf, inferior; L, left; MDD, major depressive disorder; mid, middle; parahippoc, parahippocampal; R, right; sup, superior.

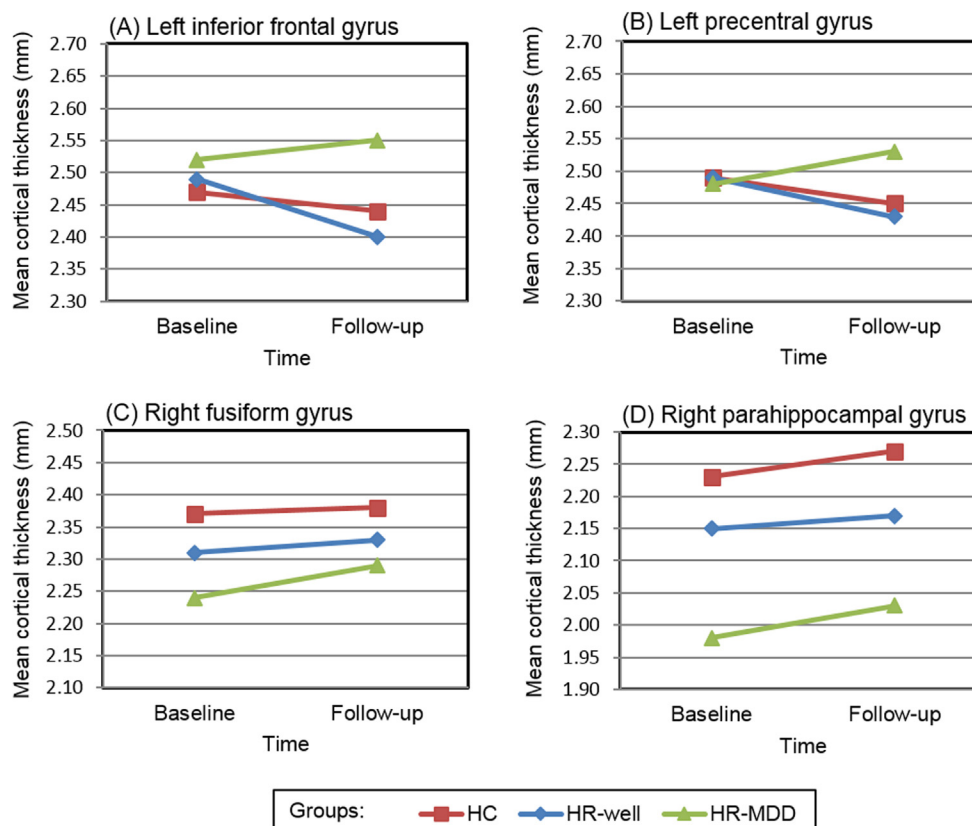


Figure 2. Significant group effects and group-by-time interactions. Significant group-by-time interactions were observed for the left inferior frontal gyrus (A) and the left precentral gyrus (B). Individuals at high risk (HR) for mood disorders who were well at baseline and remained well during the follow-up period (HR-well) showed more pronounced thinning of both brain regions as compared with the unaffected healthy control subjects (HC) over time, while the individuals at high risk for mood disorders who were well at baseline but developed major depressive disorder (MDD) during the follow-up period (HR-MDD) showed cortical thickening of these areas over time relative to the HR-well subjects. The thickening of the left precentral gyrus in the HR-MDD group was also significantly distinct from the observed thinning in the HC subjects. Significant group effects across time were observed for the right fusiform gyrus (C) and the right parahippocampal gyrus (D). HR-well and HR-MDD subjects displayed reduced cortical thickness in these regions relative to HC across time, with the HR-MDD group having more pronounced right parahippocampal thinning than the HR-well subjects.

group as compared with control subjects across both time points.

A significant group-by-time interaction ($p_{FDR} \leq .05$) was detected for the left inferior frontal gyrus ($p \leq .002$) and the left precentral gyrus ($p \leq .001$). For the inferior frontal region, HR-well subjects had a greater cortical thickness decline (3.61% thickness decline) relative to HC individuals ($p_{Bonf} \leq .002$; 1.22% thickness decline) over time and exhibited a distinct pattern of cortical thickness development as compared with the HR-MDD group ($p_{Bonf} \leq .002$) that showed an increasing thickening over time (1.19% thickness increase). For the left precentral gyrus, HR-well subjects exhibited greater cortical thickness decline (2.44% thickness decline) relative to HC individuals ($p_{Bonf} \leq .032$; 1.61% thickness decline) over time, while the HR-MDD group showed cortical thickness expansions (2.02% thickness increase) over time, which was in contrast to the regional thickness decline observed in HC ($p_{Bonf} \leq .001$) and HR-well ($p_{Bonf} \leq .001$) subjects.

No significant effects of time were observed. Nominal significant group effects and group-by-time interactions are described in Supplement 1.

Prediction Analysis

To assess whether the observed longitudinal group effects for the right parahippocampal and fusiform gyrus were also predictive at baseline assessment for a subsequent onset of MDD, additional analyses of covariance were performed for cortical thickness of these ROIs at baseline (Table S1 in

Supplement 1). There was a significant group effect for right parahippocampal ($p \leq .011$) and right fusiform thickness ($p \leq .025$). Post hoc pairwise tests indicated that the HR-MDD group had reduced right parahippocampal thickness as compared with HC participants ($p_{Bonf} \leq .010$), with no thickness differences between the HC and HR-well group ($p_{Bonf} \leq .251$) and only at the trend level between the two high-risk groups ($p_{Bonf} \leq .114$). Post hoc tests for the right fusiform gyrus revealed no significant pairwise group differences ($p_{Bonf} \leq .086$ for HC versus HR-well; $p_{Bonf} \leq .062$ for HC versus HR-MDD; $p_{Bonf} \leq .559$ for HR-well versus HR-MDD).

Correlation Analysis

There were no significant FDR-adjusted correlations between the ROIs with depression severity as measured with the HAM-D total score (Table S2 in Supplement 1).

Analysis of Potential Confounders

All results remained significant after FDR correction when randomly excluding related subjects (Table S3 in Supplement 1). For the right parahippocampus and fusiform gyrus, there was a significant group effect ($p \leq .002$ and $p \leq .009$, respectively). Significant group-by-time interactions were observed for the left inferior frontal and precentral gyrus ($p \leq .002$ and $p \leq .001$, respectively).

Moreover, all results remained significant when excluding medicated subjects (Table S4 in Supplement 1). There was a significant group effect for the right parahippocampus

($p \leq .001$) and fusiform gyrus ($p \leq .009$). Group-by-time interactions for the left inferior frontal and precentral gyrus were observed ($p \leq .005$ and $p \leq .001$, respectively).

DISCUSSION

This is, to the best of our knowledge, the first prospective longitudinal study examining structural brain changes in individuals at high risk of mood disorders who were unaffected at initial assessment and either developed MDD or remained well during the 2-year follow-up period. We report reduced cortical thickness in the right parahippocampal and fusiform gyrus across the two time points in both high-risk groups relative to control subjects, with the HR-MDD group displaying a thinner parahippocampus gyrus than the HR-well group. Over time, HR-well subjects had progressive thickness reductions in the left inferior frontal and precentral gyrus relative to control subjects, while the HR-MDD group showed cortical thickening of these areas.

Our finding of a thinner parahippocampal and fusiform gyrus in high-risk individuals suggests that thinning in these temporal brain regions constitutes a familial trait marker for vulnerability to mood disorders. Whether these structural brain abnormalities are a consequence of shared genetic and/or environmental effects cannot be determined from the data. Given that they are already present in early adulthood, they are unlikely to be of degenerative origin but likely represent disturbances of normal brain development predisposing to illness. Since the HR-MDD subjects displayed a thinner parahippocampal gyrus than the HR-well group over time, these reductions may, in addition, be related to risk of developing MDD. In line with this, our subsequent analyses revealed that reduced parahippocampal thickness in the HR-MDD group was already evident to some degree at baseline assessment before onset of depression. This cross-sectional analysis revealed group-level significance; however, subsequent pairwise comparisons indicated differences in parahippocampal gyrus between the HR groups only at the trend level of significance and therefore should be viewed as preliminary.

Previous studies support the possibility that right parahippocampal and fusiform thickness reductions are linked to increased vulnerability for mood disorders. Right parahippocampal thinning has been associated with higher genetic liability to BD (43), and research focusing on candidate genes for mood disorders has detected associations between risk allele carriers of the *DISC1* or *BDNF* gene and reductions in parahippocampal volume/thickness and fusiform volume (44,45). Right parahippocampal thinning has been observed in BD patients (22) and right fusiform thinning has been observed in a BD cohort (21,23). The few studies investigating cortical thickness in MDD have not detected similar findings (20,24,25,27–30,46–48), but since they included predominantly medicated and/or older adults, it is likely that age, medication, or duration of illness effects accounted for this discrepancy. In keeping with this, a recent voxel-based morphometry meta-analysis indeed showed that only first-episode, mainly medication naïve MDD patients have decreased gray matter in a cluster encompassing the right parahippocampal gyrus (10). Longitudinal studies by Frodl *et al.* (49,50) highlighted that hippocampal volume in MDD

patients increased in response to a 3-year antidepressant therapy and that relatively small hippocampal volumes were found in nonremitted as compared with remitted patients. Moreover, fusiform thinning in high-risk of depression individuals because of a close family history of MDD has been found to be associated with higher depression severity (51).

The parahippocampal gyrus is of particular interest for the etiology of mood disorders because of its potential role in emotional regulation. Functional MRI studies applying facial affect processing paradigms found that BD and MDD patients have increased activation in the right parahippocampus as compared with control subjects (52). Our research group has recently shown that individuals with a high risk of mood disorders who are homozygous for risk haplotype of the *DGKH* gene show relatively greater brain activation of the right parahippocampus during a verbal fluency task as compared with low-risk haplotype subjects, with the reverse pattern being observed for healthy control subjects (53). Furthermore, it has been shown that remitted depressed patients maintain an increased connectivity of the posterior cingulate cortex with the parahippocampal gyrus and that greater connectivity appears to represent a prognostic factor for future depressive episodes (54).

One plausible explanation for the right-lateralized findings may be related to the possible dominance of the right hemisphere in emotional processing [for a review, see (55)]. The reduced cortical thickness in the parahippocampus and fusiform gyrus may thus be reflecting early right hemisphere-specific brain development abnormalities in regions that are playing a distinct role in emotional processing, thereby increasing vulnerability for mood disorders.

Our analysis yielded significant group-by-time interactions for the left inferior frontal and precentral gyrus. The finding of abnormal thinning in these brain areas in the HR-well group over time relative to control subjects suggests that thinning in regionally specific left frontal lobe areas forms a familial trait marker for vulnerability to mood disorders and that abnormal thinning already takes place in early adulthood, potentially reflecting early neurodegenerative processes.

Our results are in line with a twin study that found liability for BD to be associated with inferior frontal and precentral gray matter density reductions (56), with the precentral gray matter reductions being limited to the right hemisphere. Despite potential differences in underlying environmental and genetic risk factors, cortical thinning in both of these frontal areas has also been observed in a cohort of unaffected relatives of MDD patients, with the inferior frontal thinning being restricted to the right hemisphere (51). Also, reduced gray matter volumes of the left precentral gyrus have been detected in individuals at high risk of MDD because of negative cognitive styles (57). Moreover, our findings are in concert with several neuroimaging studies reporting cortical thinning or gray matter volume reductions in the circumscribed brain regions in BD (12,19,22,23,31,58) and MDD patients (20,57).

Importantly, we observed a distinct pattern of increasing relative cortical thickness over time in the HR-MDD as compared with the HR-well group due to an absence of regional thinning of the left inferior frontal and precentral gyrus in the HR-MDD cohort. For the precentral gyrus, the cortical thickness development in the HR-MDD group was also

significantly different from the HC subjects. Since our results remained significant after excluding medicated individuals, the observed findings in the HR-MDD group cannot be attributed to medication effects but rather appear to be linked to the onset of illness and underlying disease-associated processes. Given that human brain maturation involves frontal gray matter loss beyond adolescence (59), the absence of cortical thinning in the HR-MDD group may reflect a lack or delay of normal synaptic pruning processes.

Although these findings are in contrast to the frequently observed thinning or gray matter decrease in MDD patients, they are in line with two of the three existing longitudinal studies of MDD patients that found cortical thickening of frontal or temporal brain structures over time (46,60) and with recent findings of cortical thickening of various brain areas in MDD patients (24,26,27,30). Interestingly, our findings overlap with a longitudinal study of pediatric prodromal BD subjects, displaying gray matter increases in the left ventrolateral prefrontal cortex (including the inferior frontal gyrus) over time as they convert to BD (61).

The strengths of this study are its longitudinal nature, the assessment of subjects before illness onset, the relatively young age of the participants, and the comparatively large sample size of high-risk subjects and control subjects. In addition, all subjects underwent careful clinical assessment at both time points and the effects of medication and relatedness of subjects were ruled out. All brain scans were obtained at the same scanner using the identical protocol at both visits and the MRI data were processed in an identical way using thoroughly validated methods.

Nevertheless, some limitations need to be addressed. First, it remains unknown whether currently unaffected HR-well subjects may develop MDD in the future. Second, previous longitudinal studies have reported that the majority of the high-risk subjects who developed BD themselves experienced depressive episodes years before conversion (62,63), so it appears likely that some of our HR-MDD subjects may develop BD in the future. The follow-up assessments of our study cohort will clarify if some of the HR-MDD participants will convert to BD and if some of our HR-well subjects will go on to develop a mood disorder. Third, our study groups differed with respect to depression symptom severity at baseline. However, the median of the HAM-D total score was only 1 in the HR-MDD group, suggesting only subsyndromal depression symptoms. Moreover, our correlation analysis revealed no relationship between depression symptom severity and our structural brain measures. Therefore, it appears unlikely that general mood differences at baseline between the groups have influenced our findings. Fourth, the precise onset of MDD has not been assessed, so it remains unknown if the duration of the depressive episode until the second MRI scan was conducted might have influenced the results.

In conclusion, our findings suggest that reduced cortical thickness in right parahippocampal and right fusiform gyrus across time constitutes a familial trait marker for vulnerability to mood disorders. Moreover, enhanced liability to mood disorders is associated with abnormal left inferior frontal and precentral gyrus thinning in early adulthood, potentially reflecting early neurodegenerative processes. By contrast, the onset

of MDD is linked to initially thickening of these brain areas, possibly linked to disease-associated processes through a lack of synaptic pruning. Although further longitudinal studies are required to determine their validity, these findings advance our understanding of the neuropathological processes underlying mood disorders. Future longitudinal studies should particularly investigate the course of cortical thickness development before and after the onset of depression using longer time intervals.

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